THE LACNETS PODCAST

With Martin Auerbach, MD
Released on May 15, 2022

Transcription:

Lisa Yen
Welcome to The LACNETS Podcast. I'm your host, Lisa Yen. I'm the LACNETS Director of Programs and Outreach, as well as a caregiver and advocate for my husband who is living with NET. In each podcast episode, we talk to a NET expert who answers your top 10 questions. This podcast is for educational purposes only and does not constitute medical advice. Please discuss your questions and concerns with your physician. Welcome, everyone! Thank you for joining us for this episode of The LACNETS Podcast. I'm really excited to introduce our special guest Dr. Martin Auerbach. Dr. Auerbach is a nuclear medicine specialist who received his medical degree from the University of Vienna, and he oversees the UCLA Theranostics Program as the Director of Nuclear Medicine. The program involves a diagnostic DOTATATE scans that's very familiar to the NET community, and the peptide receptor radionuclide therapy, also known as Lutathera. He's very active in research and in the UCLA multidisciplinary NET tumor board. And on a personal note, I'm very familiar with Dr. Auerbach because he's been involved in my husband's care. Welcome, Dr. Auerbach! If you could tell us a little bit about yourself and what first interested you in NETand what you do now.

Dr. Martin Auerbach
Hi, Lisa. Thank you for inviting me. And it's a great pleasure to talk to your audience. They're all very knowledgeable and always have interesting and good questions to ask. My background, as you know, I studied medicine in Austria, and then did all my postgraduate training here in the US, starting with three years of Internal Medicine in New York, and then joining the UCLA nuclear medicine team here in 2002. So I've been practicing nuclear medicine for almost 20 years now. PRRT has been around for a long time, but not in the US. So most of the treatments and research was done in Europe. But because our department has lots of connections to European centers and European researchers, we learned about this and invited them to come to our department and learn from them. Then, we were able to establish the theranostics clinic and procedures here at UCLA. And we've been doing PRRT now for a while, at least five years I think now. Initially involved in an expanded access protocol. And then of course, once it became available, clinically, been seeing a lot of patients. Nuclear Medicine used to be a primarily diagnostic discipline. But with my background of medicine, I was always interested in treatment. So that was kind of a natural fit for me, and when PRRT came along, to get involved in that and act like a real doctor, not just one looking at pictures.

Lisa Yen
That's funny. And how lovely that is. It's true, right? You're able to combine the two – look at pictures and treat people.

Dr. Martin Auerbach
It's intellectually interesting. But it's also very satisfying. I enjoy talking to patients, taking care of them and helping them as much as I can. So it's a really good fit for me.

Lisa Yen
How wonderful it is, you're able to come out of the dark room and interact directly with patients.

Dr. Martin Auerbach
It still all takes place in the basement here at UCLA.

Lisa Yen
Still a dark room, and in that dark place you're able to provide therapy as well. Well, thanks for sharing that background and trivia also. And as we move forward into these 10 questions, the first question is who's eligible for PRRT? And when considering PRRT, is there a minimum or maximum tumor size?

Dr. Martin Auerbach
So the eligibility for PRRT requires that the neuroendocrine tumor is well differentiated. Usually PRRT is not a first line treatment. So these patients usually have undergone surgery, initially, and then they develop metastatic disease, and then they've received, usually, somatostatin analogs. And then also additional treatments with Everolimus or CAPTEM, and they've failed either one or two lines of therapy. Disease has progressed. It is well differentiated, than PRRT is an option. Size, there is no maximum or minimum tumor size that we will treat or not treat. So size is not really an issue.

Lisa Yen
That's reassuring. And as you know, this is a hot topic. So I know you said well differentiated is an eligibility for PRRT. And what about age or are any other factors?

Dr. Martin Auerbach
So age is not a factor. I would say that what conditions called performance status, also known as ECOG, does play a role and you don't want to treat somebody who is already, unfortunately, at the end of their life. It's not a curative treatment, but it has a good track record in keeping the disease in check and prolonging life. But if somebody is at the end of the journey, then PRRT should not be given and won't have any benefit. And it does involve significant effort from the side of the patients having to come to the clinic. It's not free of side effects both clinically and also financially. So I think that would be the only real reason for not giving PRRT to somebody who is otherwise qualified to get it.

Lisa Yen
Okay, you're saying it shouldn't be end of life care or palliative at the very end? And perhaps maybe use it a little earlier?

Dr. Martin Auerbach
Yes.

Lisa Yen
Well, the next question would be, how do you decide on doses of radioactive agents in PRRT, and do consider people's weight? Or does everyone gets the same dose?

Dr. Martin Auerbach
So there's two things to answer this question. One is what the FDA approved, which is a fixed dose regimen. So right now, patients get the standard dose, which is 200 millicuries, regardless of weight, body habitus rate or extent of disease. There is a reduced dose of 100 millicuries in patients that have significant side effects, and we have to reduce the dose. But other than that, there is no variation for the dose that we give. Now, would we like to try something different than give a dose based on what we call dosimetry, where we can measure what the maximum dose would be that a patient can get without damaging other organs? Yes, we're very interested in that. Although there is no definitive data from little research that exists, whether that really helps or not. So it would be interesting to find out if one can improve outcome by doing dosimetry. The doses that we do give are probably sufficient and ample. What happens is when you administer the activity to the patient to treat activity, meaning the treatment dose, most of the patients pee out, so very little actually remains in the body that's being taken up by the tumor. So the doses that we currently give as dictated by the FDA approval are probably sufficient and redundant enough to treat the tumor. But the definitive answer, whether doing dosimetry and being able to give higher doses would have additional benefit for the patient? The answer to that is not out yet. And would be interesting to have.

Lisa Yen
That's really helpful. And I'm glad that you brought up dosimetry. I know you said that perhaps people might be able to get higher doses. I know that a common concern that comes up are for people who might have to get lower doses for various reasons. And they're concerned about what does it mean that PRRT will be less effective if they're getting less?

Dr. Martin Auerbach
So we don't give lower doses. We give the standard dose, and that is the dose that has been shown to be safe through a wide range of patients with different weight, different extent of disease. And it's safe. Giving a lower dose, and that only makes sense, as I said earlier, when patients have significant side effects that require a dose reduction, but other than that, we don't give lower doses.

Lisa Yen
So when they have to have the dose reduction, say 100 millicuries, because significant side effects or their labs, what would you say if they're concerned about the effectiveness?

Dr. Martin Auerbach
It's probably effective enough, again, because we are giving redundant doses where most of it is effectively peed out after the administration. So but definitive answer, nobody knows.

Lisa Yen
Thanks for that. There's so much work to be done, I'm sure. And it's exciting that we are moving forward, hopefully, in that learning process of it. So the third question is, what are the side effects of PRRT and how are they managed?

Dr. Martin Auerbach
The most important side effect really is a temporary decrease in blood counts. What happens is that some of the radioactive isotope from the PRRT goes to the bone marrow and it affects cells there that produce white blood cells, which are important to prevent infection. It affects cells that produce the red blood cells, which if they become too low, patients develop anemia. And it affects the cells that produce the platelets, which are important to prevent bleeding. Now, it's rare that there would be a severe decrease of blood counts, usually what happens is that the counts decrease a little bit, and then they recover again before the next treatment. So what we do in between treatments is we check the patient's blood counts to make sure that they're able to get the next cycle. If the blood counts go down significantly to a dangerous level, then patients develop an infection because they don't have enough white blood cells. Infection can be treated with antibiotics. If the red blood cells become too low, and the patients are severely anemic, that can be treated with a blood transfusion. And you can also give transfusions for platelets, if that is needed. Then if that happens, if patients have a severe decrease, that would then subsequently require a decrease in the PRRT dose. Instead of 200 millicuries they would get 100 millicuries.

Lisa Yen
Thanks for that and I know you've already touched on how that might affect things, as I asked that earlier. So going back to PRRT and then juggling other things, including somatostatin analogs, do you continue with somatostatin analogs? And if so, when should someone receive it?

Dr. Martin Auerbach
Excellent question. So most patients that we see are on a somatostatin analog, and we continue it during PRRT. But the recommendations are there should be four weeks between the injection of the somatostatin analog and PRRT. So the way we schedule injections and PRRT is that patients get their injection, the somatostatin analog, four weeks later they'll get their PRRT. And then right after the PRRT, within a couple of hours, you can get your next somatostatin analog injection. Four weeks later, you get your next somatostatin analog. And then four weeks later, you have your next cycle of PRRT since there are eight weeks between PRRT cycles. And that continues until the four cycles of PRRT are completed. So yes, you stay on your somatostatin analog, but we made sure to schedule everything. So there's about four weeks between somatostatin analog injection and a cycle of PRRT.

Lisa Yen
That takes some coordinating sometimes with the somatostatin analogs and PRRT.

Dr. Martin Auerbach
Yes, coordination is key. Not only with PRRT, generally in medicine. But we have good administrative staff and nurses. We communicate with doctors who refer us their patients to make sure that everything works out. And sometimes they'll be only three weeks or there'll be five weeks. It's not an issue. So it doesn't have to be exactly four weeks.

Lisa Yen
Yeah, that's helpful to know there's some margin there. The next question is, can people have carcinoid crisis with PRRT? And if so, how is it treated?

Dr. Martin Auerbach
Patients that have had carcinoid crisis or that have significant symptoms from the neuroendocrine tumors can theoretically develop a carcinoid crisis. If it happens, it usually happens during the first cycle and at the time of administration or shortly thereafter. So if it should happen, it happens at a time when the patients are still in the clinic and you can treat the carcinoid crisis. The standard treatment, although there is no definitive standard, but usually the best treatment is to give short acting somatostatin analogs IV and that usually reverses the symptoms very quickly. And supportive measures include IV fluids, sometimes H2 blockers, but the mainstay of treating a carcinoid crisis is somatostatin analogs given as a bolus injection and then either additional bolus injections until symptoms resolved or continuous IV drip. How often does it happen? I think we had one patient very early on when we started with PRRT that had to go to the emergency room. But since then, I've not seen any carcinoid crisis. And we do ask patients during the consult whether they've had carcinoid crisis before, how severe their symptoms are from the neuroendocrine tumor. So we are prepared in case there should be a patient that is more likely to develop the carcinoid crisis than other patients.

Lisa Yen
Sounds like you're prepared and ready in case it happens. I know you talked a little bit about labs and what you're looking for in a dip, when, and how often, are labs done? And which labs might be drawn? And what are you looking for?

Dr. Martin Auerbach
If a patient has normal labs to begin with, or near normal labs, then we'll just check labs two weeks before the next cycle. That's usually the time when when counts have recovered again. And we also need a little bit of leeway to order the next dose. Since it's not produced here, it has to be shipped from Italy. So there's a lot of logistics involved, we don't want to wait too long to have the labs and then have to cancel or whatever. So routinely, we check two weeks before the next cycle. In patients that have critical labs or low labs to begin with, we might check labs more frequently. The labs that we check are what we call a CBC, a complete blood count with differential that breaks down that individual white blood cells, red blood cells, platelets, and some other parameters. It gives us the numbers. We also check the kidney function to make sure that there is no damage to the kidneys, which we haven't seen. But it's still part of the routine lab. So complete blood count and a complete metabolic panel it is called.

Lisa Yen
I'm just curious, is there a cut off for the platelet and other counts that you're looking for within the CBC?

Dr. Martin Auerbach
There is something called the CTCAE. It's a standardized form of quantifying and qualifying decreases in blood counts. And there's level 1, 2, 3 and 4, depending on how severe it is. I don't know all the numbers from the top of my head. But based on that, we either continue with a treat or we have to postpone it until the decrease has resolved and counts come up again. And then you have a reduced dose. It's not willy nilly. Whatever anybody decides there are clear parameters that we use. So everybody's on the same page. Parameters that have been clinically established.

Lisa Yen
Thanks for that. That's reassuring to hear that this is a standard. And there's a clear formula that everyone's following. So what about imaging? When you do imaging, and which imaging would you do?

Dr. Martin Auerbach
First of all, imaging is usually not recommended until about three months after the last cycle. At least that's the way it's recommended now. The reason for that is that you can get in about 10% of patients the tumor can look bigger after treatment, before it actually shrinks. And that probably has to do with inflammation and swelling that occurs when tumor cells are killed. That said, if somebody has significant clinical symptoms that require doing a scan to find out what is causing the symptoms, then of course, we'll image earlier. What type of scan? There's no consensus as of now, but I usually recommend at least the first scan after the treatment should be a DOTATATE PET CT. And then that can be alternated with regular anatomical imaging, depending on what the baseline was, CT or MRI, whatever is available. It can be either or both. In patients that have liver only metastatic disease, you could argue that you don't need to do the DOTATATE PET CT because you can clearly define these lesions anatomically with MRI or CT. However, if you do dedicate anatomical imaging of the abdomen or pelvis, you might miss something that has developed outside of that area or in the bone, which is difficult to see on anatomical imaging, regardless of what imaging modality you choose, and usually the schedule is three months than six months than one year, everything looks stable or smaller. You should at least include, at some time points, dotatate PET CT to make sure you're not missing something that's developing outside the field of view anatomical imaging, which is usually limited to the abdomen, pelvis or chest.

Lisa Yen
That's helpful. And that actually leads into the next question, when would you expect to see a response with PRRT? I'm also curious if there's a maximum, a peak time to see that response. And then what's the statistics about the shrinkage or response that's expected?

Dr. Martin Auerbach
PRRT, I always explained to my patients, unfortunately, it's not a cure, but it helps in keeping the disease in check. So it prolongs time to what we call progression. And it has also shown to prolong overall survival in about 25% of patients, and just roughly breaking it down into quarters. We do see shrinkage or things getting smaller. In another 50% of patients things stay the same. We kind of arrest the disease or stop the disease from getting worse. And then unfortunately, it's also 25% of patients where PRRT does not work. We don't have any really reliable tools at this point that tell us, okay, this patient is going to benefit from PRRT, and this patient is not going to benefit from PRRT. There are some things that can hint at what's going to happen, or what to expect, or what is more likely to happen, but no definitive parameter that will tell us this patient should not get PRRT because they won't respond. So usually by three months or six months, things are getting smaller, that's when they should start getting smaller. So it takes a couple of months, at least before you see the effect.

Lisa Yen
Is there a time at which it would stop shrinking?

Dr. Martin Auerbach
That's hard to answer because when the big study, the NETTER-1 trial, which was published in New England Journal of Medicine, it's always a range of all patients. So for one specific patient, tell him okay, this is gonna work for this in this time, and then it will progress again, that's hard or impossible to predict. I'm going to have to look at my cheat sheet because I don't know the numbers from the top of my head. But if you look at the NETTER-1 trial, the progression free survival at 20 months was 65,

about two thirds of patients did not progress or had progression free survival at 20 months. Again, I realize that this is not very helpful number for patients. What do I do with this number? I would say roughly you can expect if it works, then it works for at least a year or two in stabilizing the disease. And that includes the patient where it gets smaller before it starts getting bigger again, but then again, the distribution is so that you have patients where it's much shorter, and you also have patients where the effect lasts much longer.

Lisa Yen
I'm glad that you already addressed that question that everyone would have, which is, how do I know where I'm going to fall in that curve, which bucket?

Dr. Martin Auerbach
Unfortunately, before giving the PRRT we don't know. We really have to give it and then see what happens.

Lisa Yen
You have now treated many people with PRRT. For those who have received four doses of therapy, what happens at the time, if and when there is progression, can PRRT be repeated? Can people have more than four doses of Lutathera?

Dr. Martin Auerbach
Yes, we can do what is called salvage PRRT. In patients that had initial good response. What do we call a good response? We want to see arrest or improvement that lasts for at least 12 months. That's the minimum we want to see before considering giving somebody salvage PRRT. Now, looking at the data that's available, the longer or the better, a patient responds to the initial PRRT, the better their response will be with salvage PRRT. Salvage PRRT is usually given as two cycles. And the other piece of information is that salvage PRRT works, but it doesn't work as well as the first time around.

Lisa Yen
You said two more doses. Is the same interval and the same dose?

Dr. Martin Auerbach
Yes. It's 200 millicuries, again, given eight weeks apart as two doses. And even that can be repeated. So we've had patients that have received salvage therapy twice. So if the second response is just as good again, even if it's not as good as the first time, but if it is, again, more than 12 months, then you can give it again.

Lisa Yen
Thanks for that. And as you and I know, my husband was one of those. We've been down that road together. So thanks for that. And the last question is, so we're talking about repeating PRRT or different treatments with PRRT, what's the difference between alpha and beta PRRT? I know this is a big question, but what is the difference? And how would you decide between alpha or beta PRRT?

Dr. Martin Auerbach
So right now only beta PRRT is available. Beta refers to the mode of decay of the radioactive isotope, lutetium 177, which is the radioactive isotope contained in Lutathera. Decays by emitting electrons, that's what's called beta decay. Alpha decay are radioactive isotopes that disintegrate by emitting alpha

particles, which is basically a helium molecule. So alpha particles have the advantage of being able to transfer much more energy to the targeted tumor cells. And the distance that they travel is much shorter. So the hope is that using alpha emitters, such as actinium-225 or bismuth-213, which are complexed into the dotatate that binds to the somatostatin receptors, that will improve the effect of PRRT. There's still only limited data available, some of it is spectacular, but you always have to be very careful with early data. It usually or often is spectacular, and then once applied to a larger population, the "spectacularness" - is that a word? - kind of fades away. But just from a physics and biological perspective, being able to impart a higher energy dose to the tumor cells will cause increased DNA damage and be better able to kill the tumor cells. The downside, of course, is side effect wise, are the side effects more severe? Does it affect the bone marrow more? Do you have a higher decrease in blood counts? Does it affect other organs in the body? Preliminary data shows that it's safe. But currently, it's all still research. There's no clinical application or clinically approved therapeutic at this point. We were chosen as one of the sites for an upcoming trial that uses an alpha emitter. It's still all in preliminary process. But here the indication will be that patients that have failed traditional PRRT, Lutathera, are candidates for the alpha-emitting compound. So that trial will answer important questions, but there's still a lot of work to be done before alpha emitters can or might become clinical reality.

Lisa Yen
It looks like there's a lot that we now know. There's a lot of work that has been done, and there's a lot that we don't yet know. So in closing, I'd love to hear any closing thoughts or any words of hope that you have for the NET community?

Dr. Martin Auerbach
Well, we've come a long way from days when only somatostatin analogs were available. So there's lots of tools. It's not only PRRT that is available to neuroendocrine tumor patients. You shouldn't forget that. There's also treatments that are already established, and there's lots of research going on in targeted treatments. There's lots of research going on in combining the different treatments to PRRT with immunotherapy or PRRT with chemotherapy or the mild chemotherapy that we have for neuroendocrine tumor patients. A lot of these trials are ongoing, and I'm hoping that there will be good results that will make PRRT and the other treatments synergistically more effective in neuroendocrine tumors than the individual treatments that we're applying right now. I think that's the most promising future for neuroendocrine tumors, combination of targeted therapies, whether it's molecular targeting or molecular radioactive targeting as in theronostics and PRRT. But there's lots of work going on and there will be new things coming up. And some of it will be very effective in helping patients with neuroendocrine tumors.

Lisa Yen
Thank you for that. Thank you for the hope with new treatments that are on the horizon. And it's really inspiring all the dedication and hard work that you and others, like you, are doing in this field because if it weren't for all your hard work and dedication, we wouldn't be where we are today. We wouldn't have the options that we have. So thank you for all your hard work, not just with diagnostics and therapy and the whole theranostics and also research and networking and keeping abreast and then educating all of us. Thank you on behalf of LACNETS and whole NET community for joining us today.

Dr. Martin Auerbach
It's always a pleasure talking to you and patients. It's always very informative and I always learn a lot from the questions that patients bring to me.

Lisa Yen
We are grateful for you. Thank you. Thanks for listening to The LACNETS Podcast. We want to thank our presenting sponsors, Ipsen Pharmaceutical and Advanced Accelerator Applications. For more information about neuroendocrine cancer, go to www.LACNETS.org.